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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,677	10/22/2003	Neil M. Wolfman	08702.0093-00000	2405

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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/689,677	WOLFMAN ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,23 and 25-35* is/are pending in the application.

4a) Of the above claim(s) *6-9 and 25-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-17 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17,23 and 25-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-15-05, 7-19-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner and/or Art Unit of this U.S. Patent application has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1649.

2. The amendment filed 3-6-06 has been entered into the record and has been fully considered.

3. Claims 1-17, 23, and 25-35 are pending.

Election/Restrictions

4. Applicant's election with traverse of Group I and species muscular dystrophy in the reply filed on 3-6-06 is acknowledged. The traversal is on the ground(s) that there is no serious burden, that the inventions are similarly classified, that the inventions are not distinct as they are related via administration and activity in inhibition of GDF-8. This is not found persuasive because the search and examination of the different inventions together in a single application bears significant burden to the Examiner for the reasons of record. The inventions may be separately classified and are patentably distinct in that the administration of the distinct compounds have different outcomes, functions and effects. A reference against one may not constitute a reference against another and the claims are of different scope. It is further noted that claims 6-9 are not drawn to or related to the species election of muscular dystrophy. Applicants did not state the claims reading on the elected invention.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 6-9 and 25-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3-6-06.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5, 10-17 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the stimulation of increased muscle mass via administration of an ActRIIB-Fc fusion protein as exemplified in Example 9, does not reasonably provide enablement for the method as claimed directed to treatment or prevention of at least one degenerative disorder of muscle, bone, or glucose homeostasis via administration with a generic breadth of molecules as directed to peptides with at is at least 80% identity to amino acids 23 to 138 of SEQ ID NO:3 capable of binding to GDF-8 and an Fc portion of an antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working

examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Applicants claims are directed to peptides with greater than single amino acid substitutions, naturally occurring variants, biologically active peptide fragments and fusion proteins with an unspecified number of amino acids comprising an Fc portion of an antibody.

The specification does not enable the broad scope of the claims which encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that requisite functionality is maintained. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful in any particular use and the skilled artisan would not expect functional conservation amongst homologous sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims.

The skilled artisan recognizes that amino acid alterations may lead to differences in function. For example, the skilled artisan recognizes as noted in Skolnick et al., Trends in Biotech 18(1):34-39, 2000, and as further exemplified by Choh, PNAS 77(6):3211-14, 1990, that one or more amino acid deletions, insertions or substitutions including truncations results in unpredictable effects in the resulting biological molecule, its' biological functions, the ability to bind and/or exhibit similar activity.

Receptor function cannot be reliably predicted from protein sequence homology,

especially in the case of TGF-beta family members for which even highly homologous sequences differ substantially in structure and function across its members. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance.

Moreover, the instant specification fails to exemplify any treatment or prevention in any animal model or suitable in vitro model of diseases of a degenerative disorder of muscle, bone, or glucose homeostasis. All of the noted "examples" of the specification other than noted Example 9, fail to teach any data of the experimentation described. The effects of any construct are not noted. While the desire to test or contemplation is provided, no completion of invention is evidenced where no experimentation is carried out, no results are provided and no evidence shows that the encompassed molecules are capable of any such effect.

While the specification does note an increase in muscle mass via administration

with a particular construct (Example 9), such is not commensurate with the claims. For example, Faab et al., Human Molec. Genetics, 11(7):733-741, 2002 demonstrates an in vivo experimentation model where gene transfer was shown to be effective to inhibit muscle fiber degeneration in an animal model of duchenne muscular dystrophy. Accordingly, the art recognizes the requirement for more that a mere contemplation as in instant specification. What is required is inclusion of some sort of experimentation in a suitable in vitro and/or in vivo model where predictability of the treatment may be shown. Treatment and prevention are high standards that require data and or evidence. Faab, recognizes that Duchenne is a disease for which there is no effective treatment and prevention is clearly beyond scope for this X-linked inherited disorder, see in particular Abstract. Faab, while achieving promising results is not noted to effective for treatment or prevention of disease. It is noted that this term is inclusive of curing, where a substantial number of diseases such as Duchennes' are not currently recognized as being curable. Faab concludes only, "that long-term studies in immunocompetent mdx mice as well as in larger animal models are now required to further evaluate the potential of this gene therapy approach in the context of human disease," see in particular pp. 738, column 2, paragraph 1.

Moreover, with respect to bone and glucose homeostasis degenerative diseases, no effect is shown for ActRIIB-Fc fusion in these pathological conditions. No effects of the peptide construct are shown in bone or other metabolic tissue. Accordingly, these recitations are also not in scope with the teachings of the specification. As set forth above for TGF-beta members, the structure and function of the molecules differ

substantially. While activin is noted to exhibit effects in FSH hormonal regulation as in US 6,162,896 for example, such is not commensurate with the scope of the claims.

Further, as to the substantial breadth of the molecules, the specification teaches no structural or functional activities of the claimed peptides such as any portion that mediates GDF-8 binding, or any effect of GDF-8 binding in vitro or in vivo for the breadth of molecules as recited. Accordingly, the specification fails to teach any residues which may be exchanged while retaining requsite activity or function and fail to teach the significance or function of any particular variants. As noted above the peptide structures and their pertinent sequences are insufficiently disclosed and/or enabled to the full scope of the claim.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

8. Claims 1-5, 10-17 and 23 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of ActRIIB-Fc fusion that increases muscle

mass when provided in vivo. However, the claims as written include polypeptides comprising fragments and homologues, encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification however fails to teach any other polypeptide sequence capable of providing for the same function and/or effect, fails to teach the portion of the molecule required for GDF-8 binding function and fails to teach, any construct with the activities of treating or preventing degenerative disorders of muscle, bone or glucose homeostasis. As noted above, receptor function cannot be reliably predicted from protein sequence homology. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that sequence is indeed a species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim.

A genus claim may be supported by a representative number of species as set forth in Regents of the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can

clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

Accordingly, the claimed invention lacks adequate written description support and are rejected therefore.

Conclusion

9. No claims are allowed.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
May 15, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER

5-15-06